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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,271	09/16/2003	James McSwiggen	MBHB02-763-B(400/129))	8658

20306 7590 08/28/2006

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EXAMINER
BOWMAN, AMY HUDSON

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/667,271	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,15-18,20,29,32 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,15-18,20,29,32 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/05, 2/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group I in the reply filed on 6/13/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, applicant has cancelled claim 35, thereby obviating the restriction requirement mailed on 4/14/2006.

Claims 1, 5, 15-18, 20, 29, 32, and 36-39 are pending in the application.

Sequence Compliance

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing".

Instant claim 1 recites SEQ ID NO: 1706, which is not a valid SEQ ID NO. in the CRF that has been entered in the instant application.

A complete response to this office action must correct the defects cited above regarding compliance with the sequence rules and a response to the action on the merits which follows.

The aforementioned instance of failure to comply is not intended as an exhaustive list of all such potential failures to comply in the instant application. Applicants are encouraged to thoroughly review the application to ensure that the entire application is in full compliance with all sequence rules. This requirement will not be held in abeyance.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date of the instant claims is determined to be that of application 60/401,104, which has an effective filing date of 8/5/2002. The instant claims of application do not receive the benefit of any of the earlier filed priority documents because none of the documents teach a chemically modified double stranded siRNA wherein each strand is about 18 to about 27 nucleotides in length wherein the antisense strand comprises about 18 to about 27 nucleotides that are

complementary to HCV RNA and the siRNA comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide.

Applicant asserts that PCT/US03/05043 claims priority to 60/363,124 and 60/358,580. However, PCT/US03/05043 does not claim benefit of 60/363,124 and 60/358,580 in the continuity data. PCT/US02/09187 claims benefit of 60/363,124 and 60/358,580.

Thus, the instant claims are accorded an effective filing date of 8/5/2002. Should applicants disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist in each document.

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 5 recites, "wherein the siRNA molecule comprises one or more ribonucleotides". Since this claim is drawn to a siRNA, the molecule by nature comprises one or more ribonucleotides. Therefore, claim 5 fails to further limit claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 15-18, 20, 29, 32, and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Croatian Medical Journal, 42(4), 2001, pages 463-466), in view of Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco et al. (US 6,346,398 B1), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), and Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000).

The invention of the above claims is drawn to a chemically modified siRNA molecule comprising a sense and an antisense strand, wherein each strand of the siRNA is about 18 to about 27 nucleotides in length and the antisense strand comprises about 18 to about 27 nucleotides that are complementary to HCV RNA and are also complementary to the sense strand, and the siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. The invention is further drawn to modifications to the duplex and to a composition comprising the siRNA in a pharmaceutically acceptable carrier or diluent.

Wu et al. teach inhibition of HCV gene expression by use of phosphorothioate antisense oligonucleotides and teach introduction of the oligonucleotides via pharmaceutically acceptable carriers (see page 465). Wu et al. teach that sequence recognition of nucleic acids can provide specificity for the inhibition of HCV viral gene expression without host toxicity.

Wu et al. do not teach siRNA duplexes, deoxyabasic moieties, 2'-deoxy modifications, 2'-O-methyl modifications, 2'-deoxy-2'-fluoro modifications or terminal phosphate groups.

Elbashir et al. teach chemically modified 21-nucleotide siRNA duplexes that mediate RNA interference. The duplexes taught by Elbashir et al. comprise an antisense and a sense strand. Elbashir et al. teach 2'-O-methyl and 2'-deoxy modified siRNA duplexes (see page 6881). Elbashir et al. teach that a 5'-phosphate on the antisense strand of a siRNA duplex is required for siRNA function (see page 6886).

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Parrish et al. teach dsRNA duplexes with 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand of (see figure 5). It is now known that the long dsRNA molecules of Parrish et al. would have necessarily been cleaved to shorter modified dsRNA duplexes, 21 nt in length. Inherent anticipation does not require recognition in the prior art (see MPEP 2112 and *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003)).

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides for sequence specific inhibition of a gene target. Pavco et al. teach chemical modifications including 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from

questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

It would have been obvious to substitute a siRNA duplex, as taught by Elbashir et al. and Parrish et al, for the antisense oligonucleotide taught by Wu et al. Furthermore, it would have been obvious to incorporate 2'-O-methyl, 2'-deoxy, and 5'-phosphates, as taught by Elbashir et al., as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., into a siRNA duplex specific for HCV. It would have been obvious to incorporate inverted abasic deoxyribose, as taught by Pavco et al. into the siRNA duplex.

One would have been motivated to use a siRNA targeted to HCV instead of an antisense oligonucleotide, as taught by Wu et al. because Hammond et al. teach that using dsRNA to inhibit gene expression is a sequence specific and potent method, requiring only a few molecules of dsRNA per cell to inhibit the expression of a target gene. Wu et al. teach antisense oligonucleotide inhibition of the instantly recited target and it was known in the art at the time the invention was made that using siRNA duplexes instead of antisense oligonucleotides is preferred, as evidenced by Hammond et al.

One would have been motivated to incorporate 2'-O-methyl, 2'-deoxy, or 5'-phosphates, as taught by Elbashir et al., as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. and inverted abasic deoxyriboses, as taught by Pavco et al. into the siRNA duplex targeted to HCV because each of the instantly recited chemical

modifications were known in the art to enhance the delivery of oligonucleotides, as evidenced by the teachings of Elbashir et al., Pavco et al., and Parrish et al. Although each of the oligonucleotides are not specifically siRNA duplexes, each of these molecules are sequence specific inhibitors of target gene expression and each were known to face the same delivery challenges.

Further support for this is offered by Caplen, who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies, and therefore, supports the examiner's position that one would be motivated to incorporate each of the instant modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

One would have a reasonable expectation of success to design a siRNA targeted to HCV because HCV had previously been successfully inhibited with antisense oligonucleotides, as taught by Wu et al. Since a sequence specific inhibitor was known in the art at the time the invention was made to successfully target and inhibit the instantly recited target, one would reasonably expect for a siRNA to be successful as well. Additionally, one would reasonably expect that the instantly recited chemical modifications would benefit a siRNA duplex targeted to HCV because each of the

modifications were known in the art to benefit antisense oligonucleotides or siRNA duplexes, each of which face the same delivery challenges.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 5, 15-18, 20, 29, 32, and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCaffrey et al. (Nature, Vol. 418, July 2002, pages 38-39), in view of Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Pavco et al. (US 6,346,398 B1), Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), and Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000).

The invention of the above claims is drawn to a chemically modified siRNA molecule comprising a sense and an antisense strand, wherein each strand of the siRNA is about 18 to about 27 nucleotides in length and the antisense strand comprises about 18 to about 27 nucleotides that are complementary to HCV RNA and are also complementary to the sense strand, and the siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. The invention is further drawn to modifications to the duplex and to a composition comprising the siRNA in a pharmaceutically acceptable carrier or diluent.

McCaffrey et al. teach specific, siRNA mediated inhibition of HCV expression with 21-nucleotide siRNAs. McCaffrey et al. teach successful HCV targeting with siRNAs delivered in buffer.

McCaffrey et al. do not teach chemical modifications, deoxyabasic moieties, or terminal phosphate groups.

Elbashir et al. teach chemically modified 21-nucleotide siRNA duplexes that mediate RNA interference. The duplexes taught by Elbashir et al. comprise an antisense and a sense strand. Elbashir et al. teach 2'-O-methyl and 2'-deoxy modified siRNA duplexes (see page 6881). Elbashir et al. teach that a 5'-phosphate on the antisense strand of a siRNA duplex is required for siRNA function (see page 6886).

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Parrish et al. teach dsRNA duplexes with 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand of (see figure 5). It is now known that the long dsRNA molecules of Parrish et al. would have necessarily been cleaved to shorter modified dsRNA duplexes, 21 nt in length. Inherent anticipation does not require recognition in the prior art (see MPEP 2112 and *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003)).

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides for sequence specific inhibition of a gene target. Pavco et al. teach chemical modifications including 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose.

It would have been obvious to incorporate 2'-O-methyl, 2'-deoxy, and 5'-phosphates, as taught by Elbashir et al., as well as 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., into the siRNA taught by McCaffrey et al. It would have been obvious to incorporate inverted abasic deoxyribose or phosphorothioates, as taught by Pavco et al. into the siRNA duplex taught by McCaffrey et al.

One would have been motivated to incorporate 2'-O-methyl, 2'-deoxy, or 5'-phosphates, as taught by Elbashir et al., 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. as well as phosphorothioates and inverted abasic deoxyriboses, as taught by Pavco et al. into the siRNA duplex taught by McCaffrey et al. because each of the instantly recited chemical modifications were known in the art to enhance the delivery of oligonucleotides, as evidenced by the teachings of Elbashir et al., Pavco et al., and Parrish et al. The modifications taught by Elbashir et al. and Parrish et al. were specifically utilized on dsRNA molecules. Additionally, although the modifications taught by Pavco et al. were incorporated into antisense oligonucleotides, both antisense oligonucleotides and siRNA molecules are sequence specific inhibitors of target gene expression. Each were known to face the same delivery challenges and would therefore benefit from modifications that were known to enhance delivery.

Further support for this is offered by Caplen, who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As

evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies, and therefore, supports the examiner's position that one would be motivated to incorporate each of the instant modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

One would have a reasonable expectation of success that the instantly recited modifications would benefit the siRNA duplex taught by McCaffrey et al. because each of the modifications were known in the art to benefit antisense oligonucleotides or siRNA duplexes, each of which face the same delivery challenges.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AHB

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER